## DRUG RESEARCH AND DEVELOPMENT

The development of therapies to treat infectious and immune-mediated diseases is a key component of NIAID's mission. Basic research serves as the foundation for drug development through scientific advances in microbiology, virology, and immunology. Advances in these areas help to identify potential targets for therapeutic agents and potential strategies for treating infectious and immune-mediated diseases. Through collaborations with industry, academia, and other Government agencies, NIAID has established research programs to facilitate drug development, including databases of chemical structures and chemicals that can be screened for potential use as therapeutic agents, facilities to conduct preclinical testing of promising drugs, and clinical trial networks to evaluate the safety and efficacy of drugs and therapeutic strategies.

### Division of Acquired Immunodeficiency Syndrome

The Division of Acquired Immunodeficiency Syndrome (DAIDS) devotes substantial resources to the discovery and development of new therapeutics for HIV/AIDS as well as AIDS-associated opportunistic infections, co-infections, and malignancies, attempting to focus resources on areas of promise that receive insufficient support elsewhere. A strong portfolio of basic research serves as the foundation for these activities.

Over the past 14 years, drug discovery efforts have concentrated on a relatively small number of viral targets: reverse transcriptase (RT), the enzyme that catalyzes the synthesis of viral DNA from the RNA template present in the incoming (or infecting) virion, and protease (PR), the enzyme that affects HIV maturation by cleaving and processing viral precursor proteins to their mature form. The combined use of RT and PR inhibitors (known as highly active antiretroviral therapy, or HAART) has been successful in suppressing HIV and decreasing the incidence of opportunistic infections. Nonetheless, complications have emerged with these antiviral agents, including the development of drug resistance, metabolic abnormalities and toxicities, and noncompliance due to the complexity of the required drug regimens. Moreover, damage to the immune system is only partially repaired by HAART. Recently, new classes of therapeutic agents have entered the development pipeline. These include agents that interfere with virus binding and entry into the cell as well as therapeutics directed at other viral targets such as HIV integrase, which is used by HIV to incorporate its genetic material into a host cell's DNA. Inhibition of HIV prior to integration is an attractive therapeutic strategy because it would potentially protect healthy cells from infection, thereby helping to bolster the immune system. In addition, therapeutic vaccines represent a potential new immunologic approach to complement drug treatment. Thus, while advances continue to be made, there remains an urgent need for the identification of new host and viral targets, novel drugs and delivery systems, and immunologic approaches to address the dual problems of drug resistance and toxicity.

HIV therapeutics are discovered through a number of approaches, beginning with basic research on the structure and function of viral and cellular proteins critical to the virus life cycle, immunopathogenic studies to further understand the nature of HIV-mediated immune deficiency, genetic studies to define

genes responsible for control of transmission susceptibility and disease progression, and strategies to restore or reconstitute effective immune function. These approaches are the foundation for targeted drug discovery, pursued through investigator-initiated grants, Small Business Innovation Research grants, and contracts. Current programs targeting therapeutics research on HIV/AIDS, its complications, and co-infections include Novel HIV Therapies: Integrated Preclinical/Clinical Program (IPCP); Innovation Grants for AIDS Research Program; Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program; Liver and Pancreatic Disease in HIV Infection Program; Complications of Antiretroviral Therapy Program; and International Studies of AIDS-Associated Co-Infections Program.

The IPCP supports the preclinical evaluation, development, and pilot clinical study of novel agents and strategies to suppress HIV replication, interfere with disease progression, reconstitute or repair immune damage, genetically protect cells against HIV, and ameliorate the consequences of infection. Once a novel therapeutic is identified and moves into preclinical development, the lead compound is subjected to an iterative process that improves the overall activity, safety, and effectiveness of the product. This is accomplished by additional *in vitro* testing, evaluating the agent's activity against a range of HIV isolates, testing the toxicity in different cell lines and animal models, and conducting pharmacologic studies. If appropriate, the IPCP supports early clinical evaluation in human studies.

The Innovation Grants for AIDS Research Program supports research ideas that are novel, innovative, or in the early stages of development, with the expectation that innovative research in these fields will affect understanding of the HIV pathogenesis and disease progression and provide new concepts for prevention and therapy. Targeted research for this program includes (1) therapeutic discoveries, (2) microbicide discovery, and (3) HIV pathogenesis.

The Complications of Antiretroviral Therapy Program supports research in the fundamental biochemical or pathogenic mechanisms of the metabolic complications associated with HIV disease and antiretroviral therapy. Metabolic complications highlighted by this program include lipodystrophy, insulin resistance, osteopenia, abnormal lipid metabolism, and elevated lactate levels. This program is co-sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Drug Abuse, and the National Institute of Mental Health.

The International Studies of AIDS-Associated Co-Infections (ISAAC) Program will support clinical studies of the co-infections of HIV and one or more pathogens such as tuberculosis (TB), other AIDS-defining opportunistic infections, malaria, and other parasitic infections endemic among adults and children in resource-constrained tropical countries. The long-term goals of ISAAC are to develop effective and sustainable clinical management strategies to improve local standards of care and to foster the integration of research for HIV and the relevant co-pathogens. A major emphasis will be placed on training, technology development, and enhancing independent research capacities in host country sites.

The Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program is intended to stimulate iterative preclinical research for novel therapeutic strategies against opportunistic infections, co-infections, and malignancies in people with HIV/AIDS. This program is sponsored jointly with the National Cancer Institute and the National Institute of Dental and Craniofacial Research. The AIDS-associated infections emphasized by this program are *Mycobacterium tuberculosis (M.tb), Pneumocystis carinii, Cryptosporidium parvum,* and the microsporidia. The AIDS-associated malignancies emphasized by this program are Kaposi's sarcoma, lymphomas, cervical cancer, oral warts and cancers, and anogenital cancers.

The Liver and Pancreatic Disease in HIV Infection Program is intended to stimulate research on the pathogenesis and therapeutics of the liver and pancreatic disease associated with co-infections that occur in patients with HIV infection or the metabolic complications associated with treatment of HIV infection. This program is sponsored jointly with NIDDK. The co-infections emphasized by this program include hepatitis B and hepatitis C. Metabolic complications include hepatic drug toxicity, hepatic lipid metabolism, nonalcoholic steatohepatitis, and pancreatitis.

Contract resources are also devoted to supporting clinical research on therapeutic interventions for *M.tb* infection and co-infection with HIV *(www.taacf.org)*. These interventions include high-throughput screening of anti-*M.tb* compounds and testing in animal models. For more information on research on *M.tb,* please see the section on TB on page 133.

Another important element of the DAIDS therapeutics discovery and development effort is the acquisition and dissemination of information on agents or strategies that show potential for treating HIV infection and associated opportunistic pathogens. These activities include assisting drug sponsors in obtaining additional *in vitro* and *in vivo* activity data. DAIDS also conducts a program of surveillance by developing, maintaining, and using databases of chemicals with known or potential activity against HIV and associated opportunistic pathogens. DAIDS scientific staff members use these databases to monitor compounds already under investigation and to identify additional entities to be pursued. Information from the databases is available to the scientific community on request.

Once a therapy has been developed, DAIDS conducts clinical trials to examine its effectiveness in improving the quality and duration of life for HIV-infected individuals. The trials are conducted through one of three large multicenter clinical trials networks—the Adult AIDS Clinical Trials Group (AACTG), the Pediatric AIDS Clinical Trials Group (PACTG), and the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). These programs investigate therapeutic agents and novel treatment approaches, including studies to evaluate safety, dose, activity, efficacy, and optimal use. Together, they represent the largest AIDS clinical trials network in the United States and probably in the world.

## Division of Microbiology and Infectious Diseases

The Division of Microbiology and Infectious Diseases (DMID) supports research to